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## HORMESIS IS APPLICABLE AS A PRO-HEALTHY AGING INTERVENTION IN MAMMALS AND HUMAN BEINGS

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□ The aging of the population brings new health challenges, and in particular, the need to implement suitable pro-healthy aging interventions. This paper discusses the potential of mild stressors inducing hormesis as a lifespan and healthspan extension strategy and how it can be applied to the human. There is some evidence that the anti-aging benefits of lifestyle factors, such as diet, exercise or engaging in activities may be achieved *via* hormetic regulation. This supports the validity of the concept in human. There are, however, gaps in knowledge and ethical barriers that need to be addressed to establish the suitability of the approach to the clinical context or the general geriatric population. In particular, we need to find out which stressors are safe for use as anti-aging interventions, when they have to be applied to achieve maximal benefits, how their therapeutic potential is altered by changes in the stress system induced by age and pathological conditions, and the extent to which the occurrence of adverse *versus* positive effects depends on interacting genetic and experiential factors.

*Key words* : Aging, Hormesis, Dementia, Stress system

### INTRODUCTION

The substantial increase in the mean lifespan since the 19<sup>th</sup> century is a recent phenomenon constituting an unprecedented economic challenge for modern societies (Louria 2005; Olshansky *et al.* 2007). About 15% of the population of developed countries is aged over 65; this proportion is expected to reach 20% by 2030 (12% worldwide) leading to an increased incidence of long lasting pathological states (Kinsella and Velkoff 2001), amongst which devastating dementias such as Alzheimer's disease (AD). Thus, healthy aging is a key priority. The concept of hormesis has the potential to increase our understanding of the mechanisms mediating successful aging and our ability to develop suitable interventions to achieve this.

In biological gerontology, hormesis applies to the beneficial actions resulting from a mild activation of the stress system triggering positive, adaptive effects; beneficial outcomes include enhanced coping with and ability to resist a more severe stress that might otherwise cause

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*Hormesis as a pro-healthy aging intervention*

dysfunction or disease, increased longevity, retardation of senescent deterioration and age-related disease (Masoro 2000; Mattson 2008b; Rattan 2008). To date most of our knowledge on hormetic regulation of the aging process comes from invertebrate studies and human cells in culture. The suitability of the approach in promoting healthy aging in human is yet to be established. The gaps in knowledge, challenges and barriers to the implementation of hormesis as a pro-healthy aging intervention in human will be discussed here.

### **MILD-STRESS-INDUCING HORMESIS CAN INCREASE HEALTHSPAN**

From a biological point of view, this concept makes sense and is supported by some evidence in experimental animals, but the main barrier is ethical. The general view is that stress is a harmful state, and therefore, the concept can be seen as unacceptable unless there is a clear understanding of the dose-response relationship; a concept that may be difficult to grasp at the level of the society.

Our body responds to stress by setting into motion a number of mechanisms designed to protect it from adverse health effects, e.g. enhanced immune function, neuroprotection and cognitive function. Thus, it is conceivable, and it has been pioneerly proven in rats by Frolkis (1982), that the exposure to mild stressors can strengthen the organism's defense mechanisms and result in a longer and healthier life. It is only when this response is excessive, either in intensity or in duration that adverse health effects occur. A good illustration of the validity of the concept comes from our recent work showing that the repeated exposure to a novel environment, which induces a mild stress response, is able to delay the progression of cognitive and neuropathological changes relevant to AD in a genetic mouse model (Pardon *et al.* 2009; Rattray *et al.* 2009), despite this condition being incurable. By contrast, others have found an accelerated disease progression in mouse models of AD when exposed to more severe chronic stressors, such as social isolation or repeated 6-h immobilization sessions (Dong *et al.* 2004; Jeong *et al.* 2006).

### **MILD STRESSORS-INDUCING HORMESIS SAFE FOR USE IN MAMMALS AND HUMANS.**

A number of situations qualify as potential paradigms for hormesis. Which one to use depends on several factors to include the species and long-term objectives. In rodents and other experimental animals, the intensity of the stressor can be controlled in many ways (e.g. duration, frequency, intermittence), such that it is technically feasible to test if low doses of established adverse events would trigger positive effects, as a proof of concept. It is nevertheless thought that not all mild stressors will induce hormesis, and many examples have been reported where low intensity stimulations can produce adverse effects (Calabrese *et al.* 2006).

*M.-C. Pardon*

It is therefore essential to screen in animals which interventions are able to induce hormesis in order to understand better the underlying mechanisms, regardless of their applicability to the human situation. However, when the ultimate aim is to translate animal research into clinical use, the range of potential mild stressors is limited by ethical issues. Whilst it is possible that the short-term (minutes) exposure to physical stressors such as cold, aggressive interactions or immobilization, will induce hormesis in animals, the use of similar situations in humans to promote health is unthinkable. Thus, the above question has to be addressed from an outcome perspective, i.e. are any of the established or suspected pro-healthy aging interventions paradigms for hormesis? To date, the strongest candidates for use in human are moderate exercise (Gomez-Pinilla 2008; Goto *et al.* 2007), calorie restriction (Mattson 2008a) and possibly novelty (engaging in novel social and organizational activities in human) (Pardon *et al.* 2009) or cognitive challenges (Rattan 2008).

### **CAN HORMESIS BE INDUCED IN SUBJECTS VULNERABLE TO STRESS?**

Hormesis is a very likely mechanism underlying the benefits of a healthy, active lifestyle. Thus, it could be considered as an accepted mean of achieving increased healthspan. Indeed, modern societies and a number of aging-related charities are raising awareness of the health benefits of healthy eating, exercise and engaging in activities. Although the mechanisms mediating hormetic regulation are far from being fully established, the observed beneficial outcome constitutes a sufficient proof of concept to support the application to human health.

Two key inter-related questions, however, need to be addressed prior to the systematic use of lifestyle factors inducing hormesis in a clinical context or its application to the general geriatric population.

1. Will all individuals similarly experience positive effects of mild stressors, or will the outcomes result from interacting genetic and experiential factors?
2. How and when mild stressors need to be applied to be effective and/or result in maximal healthspan benefits?

Inter-individual variability in the ability to cope with stress, due to age or other personal factors, is there a key issue. As discussed before (Pardon 2007), one may expect that because of a deficient stress system, the low resistance of subjects vulnerable to stress would be such that lower levels of stress will trigger negative effects and accelerate age-related pathologies. However, our recent work suggests that this is not the case, and even that, in some circumstances, a hormetic response is more likely to occur in individuals susceptible to stress. Indeed, genetic mouse models of AD show sign of vulnerability to stress prior to onset of pathological markers

*Hormesis as a pro-healthy aging intervention*

(Pardon 2007), but we found that the repeated exposure to mild novelty stress improved cognitive and pathological markers in such mice (Pardon *et al.* 2009; Rattray *et al.* 2009) whilst impairing memory performance in the stress-resistant C57b/16 mouse line (Scullion *et al.* 2009). Moreover, the ability to cope with stress generally declines with age, but recent evidence also suggest that age is not a key issue to the occurrence of hormetic effects of exercise in normal rats (Goto *et al.* 2007). Thus, the conditions in which hormesis will work is an intriguing question that needs to be elucidated before considering it as a suitable anti-aging strategy. This is complicated by the fact that some mild stressors may induce hormesis in a sub-population while producing adverse effects in others.

**HORMESIS MAY HELP PREVENTING OR DELAYING NEURODEGENERATIVE DISEASES.**

The mild stressors effective in extending lifespan and healthspan, such as enrichment or exercise in rodents, have also been shown to delay the progression of pathological markers in mouse models of neurodegenerative conditions such as AD (Pardon 2007) or Parkinson's disease (Pothakos *et al.* 2009). And in human, a very recent study emphasized that people who engage more in physical, social, leisure or organizational activities have a reduced risk of developing AD (Wang *et al.* 2009).

As far as dementia is concerned, pre-clinical evidence to date points towards a higher preventive than therapeutic potential of mild stress exposure. For instance, in AD mice, voluntary exercise was found to attenuate the age-related accumulation of senile plaques (mainly composed of amyloid beta peptide 42 (Abeta1-42)) when applied from prior to the onset of the amyloid pathology (Adlard *et al.* 2005). The same intervention reduced the Abeta1-42/Abeta1-40 ratio without any effect on amyloid plaque load in aged mice showing severe amyloid pathology (Mirochnic *et al.* 2009) despite still having some cognition-enhancing effects (Parachikova *et al.* 2008). The nature of the stressor may also play a role, as we found that the repeated exposure to novelty prevented the development of a memory and re-learning deficit in AD mice, but did not reverse those once established (Pardon *et al.* 2009; Rattray *et al.* 2009). This indicates that the benefits of mild stressors may decrease as the disease progresses, with still some potential for improved health.

**THE APPLICATION OF HORMESIS TO HUMANS FOR HEALTHSPAN IMPROVEMENT IS LIMITED BY GAPS IN KNOWLEDGE.**

As mentioned before, we really need to know which ethically acceptable mild stressors can provide hormetic regulation of age-related disease processes. The fact that candidate stressors emerges as being part of an active lifestyle will facilitate the implementation of the approach to the human. In addition, since hormesis act through inducing a mild stress

*M.-C. Pardon*

response, it is essential to understand the consequences that may arise when applied to an impaired stress system. It is thus critical to expand our knowledge on how the stress system age or is altered by related-medical conditions and to establish whether mild stressors can do more benefits than harm under such circumstances.

In summary, mild stressors inducing hormesis have the potential to expand lifespan and healthspan in human and even to improve incurable age-related brain diseases. The application of hormesis to the human will be facilitated by the fact that the strongest candidates are part of an active, healthy lifestyle, and are perceived as positive environmental factors. There is, however, a need to increase our knowledge on how the therapeutic potential is altered by advancing age or pathological status, prior to accepting hormesis as a suitable pro-healthy aging intervention.

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*Hormesis as a pro-healthy aging intervention*

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